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| 09/380,337 | 03/06/2000 | SETTARA CHANDRASEKHARAPPA | 15280-315100 | 2491 |

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| UNGAR, SUSAN NMN | |

| ART UNIT | PAPER NUMBER |
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| 1642 | |

DATE MAILED: 05/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/380,337 | CHANDRASEKHARAPPA ET AL. | |
| | Examiner | Art Unit | |
| | Susan Ungar | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on *03 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☐ Claim(s) *1-6,19-24,26-30 and 32-37* is/are pending in the application.

4a) Of the above claim(s) *14-18,27-29,34 and 35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-6,19-24,26,30,32,33,36 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 3, 2004 has been entered.

2. The Amendment filed March 3, 2004 in response to the Office Action of March 25, 2003 is acknowledged and has been entered. Previously pending claims 9-13 and 38-42 have been canceled and claims 1, 4, 5 have been amended. Claims 1-6, 19-24, 26, 30, 32, 33, 36-37 are currently being examined.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The following objections are maintained:

Applicant argues that there is no evidence provided that recitation of formalin with 1 mg of heparin is a conventional hybridization condition, based on US Patent No. 6,107,462 since it is not referred to in manuals routinely used in the art such as Sambrook.

The argument has been considered but has not been found persuasive. In particular, the '462 patent establishes that this hybridization condition was known and used in the art and it is clear that one of skill would not readily recognize that an obvious error had been made since the issued patent uses the same hybridization conditions with wording identical to that recited in the specification as originally filed. Applicant is required to cancel the new matter in the response to this Office Action.

4. The following rejections are being maintained:

***Claim Rejections - 35 USC 112***

5. Claims 1-3, 5, 30, 32-33 and 36-37 remain rejected under 35 USC 112, first paragraph and claims 4, 6, are rejected under 35 USC 112, first paragraph for the reasons previously set forth in the paper mailed March 25, 2003, Section 4, page 2 drawn to claims 1-3, 5, 30, 32-33 and 36-37 .

Applicant reiterates previously arguments. The arguments had been considered but had not previously been found persuasive and the rejection is maintained.

Applicant argues that those of skill in the art have identified menin proteins with 95% identity to SEQ ID NO:2 as menin proteins, even in the absence of knowledge of a specific function, this suggests that those of skill in the art are able to determine members of this genus.

The argument has been considered but has not been found persuasive because, for the reasons of record, even if they could be identified as menin-like proteins, one would not know how to use the claimed invention.

Applicant's arguments have not been found persuasive and the rejection is maintained.

6. Claims 1-3, 5-6, 19-24, 26, 30, 32-33, 36-37 remain rejected under 35 USC 112, first paragraph and claims 4 and 6 are rejected under 35 USC 112, first paragraph for the reasons previously set forth in the paper mailed March 25, 2003, Section 5, pages 2-3.

Applicant reiterates previously arguments. The arguments had been considered but had not previously been found persuasive and the rejection is maintained.

Applicant further argues that the Chandrasekharappa Declaration provides evidence of the association between the claimed nucleic acids and expressed protein sequences. Dr. Chandrasekharappa states that the expressed protein and obtained antibodies described in the specification were used to evaluate protein expression in various cells and tissues and exemplary data is presented in Guru et al, PNAS, 1998, 95:1630-1634 wherein on page 1631, column 2, the reference states that antibodies detected endogenous protein which is localized predominantly to the nuclear fraction and thus these studies provide additional evidence that the MEN1 nucleic acids encode menin protein. The argument has been considered but has not been found persuasive as the reference does not provide a nexus between SEQ ID NOS 1 and 3 and the species of Guru et al. A nexus could be provided by demonstrating that the polynucleotide encoding the polypeptide of the reference is the same as the claimed polynucleotide. It is noted that the Guru reference points to the isolation of pCMV-Sport menin clone A11 on page 1630, column 2. The rejection might be obviated, for example, by the alignment of that full length menin cDNA with the claimed cDNA, demonstrating their identity.

Dr. Chandrasekharappa further argues that Watout et al describe menin polypeptide and nucleic acid sequences with reference to Chandrasekharappa et al (Science, 1997, 404:408) and Guru et al, *Supra* wherein the nucleic acid and polypeptide sequences in the two references are the same as those in the instant application. The argument has been considered but has not been found persuasive for the reasons set forth previously and above. The rejection might be obviated, for example, by the submission of the alignment of the full length menin cDNA disclosed with the claimed cDNA, demonstrating their identity.

Applicant points to expression studies performed using menin-specific antibodies generated to peptides comprised by SEQ ID NO:2 and points to Guru et al, Antibodies Section in Materials and Methods.

The argument has been considered but has not been found persuasive. The rejection might be obviated, for example, by submission of the alignment of these amino acid sequences with those disclosed in the specification, demonstrating their identity.

Applicant argues that the identification of MEN1 as mutated in multiple endocrine neoplasia type 1 is compelling evidence of its role in the disease which is supported by the peer reviewed Chandrasekharappa et al reference, *Supra*.

The argument has been considered but has not been found persuasive, the argument raised is not drawn to the gene, but rather is drawn to a "nucleic acid encoding" which reads on degenerate sequences encoding SEQ ID NO:2. Given the lack of information regarding the function of the protein, given the lack of information as to whether the protein is expressed or differentially expressed, one would not know how to use the encoded polypeptide. The rejection may be obviated, for example, by amending the claims to delete reference to "encoding" language and claiming polynucleotides comprising SEQ ID NO: 1 and claiming polynucleotides consisting of SEQ ID NO:3 in particular since no polynucleotide other than SEQ ID NO:1/3 has been demonstrated to be mutated in multiple endocrine neoplasia type 1.

Applicant argues that one would know how to use nucleic acids encoding SEQ ID NO:2 because expression of the protein could be used to generate antibodies for diagnostic and prognostic purposes and the nucleic acids encoding

variant menin proteins can be used to generate antibodies to detect mutated proteins.

The argument has been considered but has not been found persuasive because neither the specification nor the art of record has disclosed that the protein is expressed or differentially expressed in any disease or demonstrated that it could be used for either diagnostic or prognostic purposes. In particular, if it were to be found that the polynucleotide of the Wautot et al reference is indeed the polynucleotide of the instant invention, the findings of the Wautot et al reference are particularly relevant to this rejection. Wautot et al specifically teach, on page 880, col 2 that "We did not detect any obvious alteration in menin expression levels and cellular location in LCLs carrying germ-line mutations compared with LCLs from non-affected individuals..... It appears that regulatory mechanisms maintain a constant level of expression, whether both alleles are functional or not." Further, Guru et al, 1999 specifically teaches that the amino acid sequence of "this putative tumor suppressor offers no clue to the function.....of the protein" (see abstract). Given this information, one would not know how to use the encoded protein or antibodies specific for the encoded protein.

Applicant's arguments have not been found persuasive and the rejection is maintained.

***New Grounds of Rejection***

***Claim Rejections - 35 USC 112***

7. Claims 2-4 and 32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The

written description in this case only sets forth SEQ ID No: 3 which is the complete genomic sequence of a 9.2 kb segment containing all 10 exons of MEN1 (p. 2, lines 25-29) and therefore the written description is not commensurate in scope with the claims drawn to an isolated, recombinant, nucleic acid wherein the sequence comprises non-coding regions, wherein the non-coding regions comprise introns, comprises SEQ ID NO:3 which reads on the chromosome wherein said sequences are found, wherein SEQ ID NO:3 is found.

*Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, clearly states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the written description inquiry, *whatever is now claimed.* (See page 1117). The specification does not clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed. (*See Vas-Cath* at page 1116).

Furthermore, In *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held, at section B(1), that An adequate written description of a DNA requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention.

The chromosome upon which SEQ ID NO:3 is found would be expected to have both introns and exons as well as regulatory elements associated with SEQ ID NO:3, however, other than stating that the term "genomic" also refers to any cis-acting transcriptional regulatory elements, e.g. promoters and enhancers, that regulate the expression of MEN1, no description of these elements is disclosed. Further, the chromosome upon which SEQ ID NO:3 is found would be expected to

have both introns and exons as well as regulatory elements associated with genes other than SEQ ID NO:3. The specification teaches that the boundaries of the exons of genomic polynucleotide for MEN1 are identified by comparison with the complete genomic sequence of a 9.2 kb segment containing all 10 exons. The specification does not however disclose, recite or give any guidance on the rest of the chromosomal genomic sequence upon which the 9.2 kb segment is found. Thus the structure of the broadly claimed polynucleotide is not defined. Since the structure of the isolated nucleic acid wherein the sequence comprises SEQ ID NO:3 gene is not defined and with the exception of SEQ ID NO:3, the skilled artisan cannot envision the detailed structure of the encompassed polynucleotides, conception is not achieved until reduction to practice has occurred. Adequate written description requires more than a mere statement that it is part of the invention . The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

No disclosure, beyond the mere mention of complete genomic sequence of a 9.2 kb segment containing all 10 exons is made in the specification. This is insufficient to support the generic claim.

Therefore only an isolated, recombinant, polynucleotide consisting of SEQ ID NO:3, but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph.

8. Claims 2-4 and 32 are rejected under 35 USC 112, first paragraph because the specification while enabling for an isolated, recombinant polynucleotide consisting of SEQ ID NO:3, does not reasonably provide enablement for an isolated, recombinant, polynucleotide comprising SEQ ID NO:3.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected to make and use the invention commensurate in scope with these claims.

The claims are drawn to an isolated or recombinant nucleic acid wherein the sequence comprises SEQ ID NO:3. This means the chromosome upon which genomic SEQ ID NO:3 resides. The specification teaches SEQ ID No: 3 which is the complete genomic sequence of a 9.2 kb segment containing all 10 exons of MEN1 (p. 2, lines 25-29). The specification further teaches that menin polypeptide encoding nucleic acid sequences of the invention include genes and gene products identified and characterized by analysis using the nucleic acid sequences of SEQ ID NO:1 (p. 18, lines 20-25).

One cannot extrapolate the teaching of the specification to the scope of the claims as neither the specification nor the art of record has disclosed how to use the broadly claimed invention. The claims as written are drawn to the chromosome which comprises SEQ ID NO:3. The specification does not teach which other genes are located on the chromosome or how to use the other genes that are located on the chromosome. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict how to use the claimed chromosome with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

9. Claims 30, 32-33, 36-37 are rejected under 35 USC 112, first paragraph because the specification while enabling for an isolated, transfected cell comprising said polynucleotide and an expression cassette to be used *in vitro* does

not reasonably provide enablement for a transfected cell comprising said gene wherein the transfected cell is a human cell, wherein said expression cassette refers to any recombinant expression system for the purpose of expressing a nucleic acid sequence of the invention *in vivo* in a mammalian cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected to make and use the invention commensurate in scope with these claims.

The claims are drawn to a transfected cell comprising said nucleic acid, wherein the cell is a human cell and to an expression cassette containing said nucleic acid wherein said expression cassette refers to any recombinant expression system for the purpose of expressing a nucleic acid sequence of the invention *in vivo* in a mammalian cell. This reads on *in vivo* gene therapy. The specification specifically teaches gene therapy applications with the claimed nucleic acid and expression cassette for the treatment of inherited diseases, particularly those diseases such as MEN1 where the defect is with a single gene MEN1 (see para bridging pages 45-46), thus contemplating gene therapy in humans. The specification teaches viral vectors useful for the practice of the invention (pages 46-49).

One cannot extrapolate the teaching of the specification to the scope of the claims because the specification provides neither guidance on nor exemplification of the use of the claimed invention for *in vivo* gene therapy in humans. It was well known in the art at the time the invention was made that the status of the field of gene therapy in humans was unpredictable in regard to obtaining therapeutic levels of transcription in a host subject. Orkin et al (Report and Recommendations of the Panel to Assess the NIH investment in Research on Gene Therapy, 1995) state that

"while the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol, despite anecdotal claims of successful therapy and the initiation of more than 100 Recombinant DNA Advisory Committee (RAC)-approved protocols" and further teach that significant problems remain in all basic aspects of gene therapy. In addition, Marshall (Science, 1995, 269:1050-1055) teaches that there has been no unambiguous evidence that genetic treatment has produced therapeutic benefits" (p. 1050, col 1) and that "difficulties in getting genes transferred efficiently to target cells - and getting them expressed - remain a nagging problem for the entire field" (p. 1054, col 3). James Wilson, one skilled in the art stated that "{t}he actual vectors- how we're going to practice our trade - haven't been discovered yet" (p. 1055, col 2). Culver et al (TIG, 1994, 10:174-178) reviewing gene therapy for cancer, conclude that the "primary factor hampering the widespread application of gene therapy to human disease is the lack of an efficient method for delivering genes *in situ*, and developing strategies to deliver genes to a sufficient number of tumor cells to induce complete tumor regression or restore genetic health remains a challenge " (p. 178). Further, Orkin et al reports major difficulties at the basic level include shortcomings in all current gene transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host. (see page 1). None of the available vectors systems is entirely satisfactory and many of the perceived advantages of vector systems have not been experimentally validated, for example, a major disadvantage of retroviruses is that they infect and integrate only dividing cells, a major disadvantage of the adenovirus vector system is its relatively high immunogenicity and the complexity of its genome, a major perceived strength of adeno-associated virus is its integration at a specific site in

the infected cell genome, however, this data has been confirmed only for wildtype virus (page 8). Hodgson (Exp. Opin. Ther. Patents, 1995, 5:459-468) discusses the drawbacks of viral transduction and states that "[d]eveloping the techniques used in animal models, for therapeutic use in somatic cells, has not been straightforward" (pp 5459-460). Miller et al (FASEB J., 1995, 9:190-199) also review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy there will have to be advances. Further, targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (p. 198, col. 1). Finally, the research community, as reported by Nature Biotechnology, 1997, 15:815, has responded to the issues raised in the Orkin Report drawn to vector based delivery systems, that is the critical steps of delivery of a gene to the right cell and the subsequent maintenance of gene expression, since it is now widely appreciated that the natural tropism of a virus, while advantageous to its own replication cycle is not always optimal for a gene delivery protocol and a number of laboratories have explored methods to redirect the targeting that has evolved to ensure viral infectivity in ways that may be more suitable to the aims of gene therapy and concludes that this return to first principles should help to continue to move gene therapy in the direction of its largest and most important ambitions (p. 815). Clearly, the issues raised by the Orkin report, although being addressed, have not been resolved. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to use the contemplated and claimed invention. It is concluded that in light of the quantity of experimentation necessary, the lack of adequate direction or

guidance presented, the lack of working examples, the nature of the invention, the state of the prior art with its recognized unpredictability and the breadth of the claims, it would require undue experimentation for one of skill in the art to use the claimed invention. The rejection may be obviated, for example, by amending claim 30 to recite an isolated transfected cell and by amending claim 36 to recite an expression cassette for *in vitro* use.

10. Claims 1-3, 5-6, 30, 32-33, 36-37 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

Claims 1-3, 5-6, 30, 32-33, 36-37 are drawn to an isolated or recombinant nucleic acid encoding menin, wherein said nucleic acid encodes a protein comprising an amino acid sequence having at least 95% identity to SEQ ID NO:2, wherein the nucleic acid sequence encodes a menin protein that binds to an antibody raised against a polypeptide having an amino acid sequence as set forth in SEQ ID NO:2, which reads on a polypeptide with at least 95% identity to SEQ ID NO:2. The findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that A[a] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials. Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as vertebrate insulin cDNA or mammalian insulin cDNA without more, is not an adequate written description of the genus

> because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that the written description requirement can be met by show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

Thus, the instant specification may provide an adequate written description of an isolated or recombinant nucleic acid encoding menin, wherein said nucleic acid encodes a protein comprising an amino acid sequence having at least 95% identity to SEQ ID NO:2 per Lilly by structurally describing a representative number of isolated or recombinant nucleic acids encoding menin, wherein said nucleic acids encode a protein comprising an amino acid sequence having at least 95% identity to SEQ ID NO:2or by describing structural features common to the members of the genus, which features constitute a substantial portion of the genus. Alternatively, per Enzo, the specification can show that the claimed invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

In this case, the specification does not describe the isolated or recombinant nucleic acids encoding menin, wherein said nucleic acids encodes a protein comprising an amino acid sequence having at least 95% identity to SEQ ID NO:2/binds an antibody that binds to SEQ ID NO:2 in a manner that satisfies either the Lilly or Enzo standards. Other than the cDNA, SEQ ID NO:1 and the genomic sequence of SEQ ID NO:3, the specification does not provide the complete structure of any isolated or recombinant nucleic acid encoding menin, wherein said nucleic acid encodes a protein comprising an amino acid sequence having at least 95% identity to SEQ ID NO:2/binds an antibody that binds to SEQ ID NO:2, nor does the specification provide any partial structure of such isolated or recombinant nucleic acid encoding menin, wherein said nucleic acid encodes a protein comprising an amino acid sequence having at least 95% identity to SEQ ID NO:2/binds an antibody that binds SEQ ID NO:2, nor any physical or chemical

characteristics of said isolated or recombinant nucleic acid encoding menin, wherein said nucleic acid encodes a protein comprising an amino acid sequence having at least 95% identity to SEQ ID NO: 2/binds an antibody that binds SEQ ID NO:2 nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses the cDNA, SEQ ID NO:1 and the genomic sequence of SEQ ID NO:3, this does not provide a description of said isolated or recombinant nucleic acid encoding menin, wherein said nucleic acid encodes a protein comprising an amino acid sequence having at least 95% identity to SEQ ID NO:2/binds an antibody that binds SEQ ID NO:2 that would satisfy the standard set out in Enzo.

The specification also fails to describe the isolated or recombinant nucleic acid encoding menin, wherein said nucleic acid encodes a protein comprising an amino acid sequence having at least 95% identity to SEQ ID NO:2/binds an antibody that binds SEQ ID NO:2 by the test set out in Lilly. The specification describes only the genomic and cDNA sequences of a single isolated or recombinant nucleic acid encoding menin, wherein said nucleic acid encodes a protein comprising an amino acid sequence having at least 95% identity to SEQ ID NO:2. Therefore, it necessarily fails to describe a representative number of such species. In addition, the specification also does not describe structural features common to the members of the genus, which features constitute a substantial portion of the genus.

Thus, the specification does not provide an adequate written description of the isolated or recombinant nucleic acid encoding menin, wherein said nucleic acid encodes a protein comprising an amino acid sequence having at least 95% identity

to SEQ ID NO:2/binds an antibody that binds SEQ ID NO:2 that is required to practice the claimed invention.

11. Claims 19-24, 26 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

Claims 1, 11, 16 are drawn to a method for detecting the presence or absence of a mutation in a human Men1 gene comprising a nucleotide sequence that encodes a human menin as set forth in SEQ ID NO:2 or the absence of a MEN1 allele. Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that [a] written description of an invention involving a chemical genus, like a description of a chemical species, >requires a precise definition, such as by structure, formula, [or] chemical name,= of the claimed subject matter sufficient to distinguish it from other materials. Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as vertebrate insulin cDNA or mammalian insulin cDNA without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that the written description requirement can be met by show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of a human Men1 gene, as disclosed in the specification that is involved in multiple

endocrine neoplasia-type 1 wherein the gene is mutated in numerous families that present with multiple endocrine neoplasia-type 1, or an allele thereof wherein the nucleotide sequence encodes a human menin as set forth in SEQ ID NO:2, per Lilly by structurally describing a representative number of said genes or by describing structural features common to the members of the genus, which features constitute a substantial portion of the genus. Alternatively, per Enzo, the specification can show that the claimed invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

In this case, the specification does not describe the nucleotide sequence encoding a human menin as set forth in SEQ ID NO:2 required to practice the claimed method in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of any human menin sequence except that as disclosed in the specification that is involved in multiple endocrine neoplasia-type 1 wherein the gene is mutated in numerous families that present with multiple endocrine neoplasia-type wherein said sequence is that of SEQ ID NO:1 and the genomic SEQ ID NO:3, nor does the specification provide any partial structures of the encompassed genes, nor any physical or chemical characteristics of the encompassed genes, nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses as set forth above, this does not provide a description of the nucleotide sequence encoding a human menin as set forth in SEQ ID NO:2 that would satisfy the standard set out in Enzo.

The specification also fails to describe the nucleotide sequence encoding a human menin as set forth in SEQ ID NO:2 by the test set out in Lilly. The specification describes only a single nucleotide sequence encoding a human menin as set forth in SEQ ID NO:2 and its genomic counterpart wherein as disclosed in the specification the sequence is involved in multiple endocrine neoplasia-type 1 wherein the gene is mutated in numerous families that present with multiple endocrine neoplasia-type 1. Therefore, it necessarily fails to describe a representative number of such species. In addition, the specification also does not describe structural features common to the members of the genus, which features constitute a substantial portion of the genus.

Thus, the specification does not provide an adequate written description of the nucleotide sequence encoding a human menin as set forth in SEQ ID NO:2 except that as disclosed in the specification that is involved in multiple endocrine neoplasia-type 1 wherein the gene is mutated in numerous families that present with multiple endocrine neoplasia-type 1 that is required to practice the claimed invention. Since the specification fails to adequately describe the product which is critical for the practice of the invention, it fails to describe the method of using the product.

12. Claim 32 is rejected under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 32 is indefinite because there is no antecedent basis for phrase "exogenous nucleic acid" recited in claim 30 from which claim 32 depends.

***Claim Rejections - 35 USC 102***

13. Claims 1-6, 30, 32, 33, 36, 37 are rejected under 35 USC 102(b) as anticipated by US Patent No. 4, 594,318 as evidenced by Guru et al (Mammalian Genome, 1999, 10:592-596, IDS item).

Guru et al teach that human Men1 gene is located on Chr 11q13.

The claims are drawn to an isolated or recombinant nucleic acid encoding menin wherein said nucleic acid encodes a protein comprising an amino acid sequence having at least 95% identity to SEQ ID NO:2, which further comprises non-coding sequence, wherein the non-coding sequence comprises introns, which encodes a protein having the sequence as set forth in SEQ ID NO:2, which binds to an antibody raised against a polypeptide having an amino acid sequence as set forth in SEQ ID NO:2, a transfected cell comprising a heterologous nucleic acid of claim 1, wherein the nucleic acid comprises SEQ ID NO:3, an expression cassette comprising said nucleic acid operably linked to a promoter, further comprising an expression vector.

US Patent No. 4,594,318 teaches isolated human chromosome 11 which comprises SEQ ID NO:3 and therefore encodes SEQ ID NO:2, a transfected cell comprising said chromosome, CHO-K1, which as defined by the specification is an expression vector (see attached summary of key words in action). All of the limitations of the claims are met.

14. No claims allowed.

15. All other objections and rejections recited in the previous action are hereby withdrawn.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is

(571) 272-0837. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached at 571-272-0841. The fax phone number for this Art Unit is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
May 11, 2004